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General Stress Response to Conventional and Laparoscopic Cholecystectomy

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Objective

In many retrospective and prospective observational studies, laparoscopic cholecystectomy (LC) compares favorably with conventional cholecystectomy (CC), with respect to length of hospital stay, postoperative pain, and pulmonary function, indicating a diminished operative trauma. Comparison of laboratory findings (stress hormones, blood glucose, interleukins) are a possibility to objectify stress and tissue trauma of laparoscopic and conventional cholecystectomy.

Summary Background Data

Major body injury, surgical or accidental, evokes reproducible hormonal and immunologic responses. The magnitude of many of these changes essentially is proportional to the extent of the injury.

Methods

In a prospective study, biochemical stress parameters were measured in the blood of patients undergoing elective cholecystectomy because of symptomatic cholecystolithiasis. Patients with acute cholecystitis, pancreatitis, choledocholithiasis, or malignant disease were excluded. Values from 40 patients after LC and from 18 patients after CC were compared. Both groups had similar patient characteristics, baseline values, and perioperative care, except for deeper anesthesia during CC.

Results

On postoperative day 1, epinephrine ($p = 0,05$), norepinephrine ($p = 0.02$), and glucose ($p = 0.02$) responses were higher after CC. Two days postoperatively, norepinephrine remained higher after CC ($p < 0.01$). Interleukin-1β responses were higher during ($p < 0.01$) and 6 hours after CC ($p = 0.03$). Interleukin-6 responses were higher 6 hours ($p = 0.03$), 1 day ($p = 0.02$), and 2 days ($p < 0.01$) after CC.

Conclusions

The results show significant lower values of intraoperatively and postoperatively measured epinephrine, norepinephrine, interleukin-1β, and interleukin-6 in patients with laparoscopic cholecystectomy, indicating a minor stress response and tissue trauma in this group of patients. The results correspond to the favorable results of most other trials evaluating clinical aspects of laparoscopic cholecystectomy.

Laparoscopic cholecystectomy (LC) became widely accepted by patients and physicians, despite a lack of prospective, randomized trials comparing this new technology with conventional cholecystectomy (CC). In one trial claiming a randomized design, only five patients with LC were studied, and the method of randomization was not given.[1] Another study evaluated only the pulmonary function of 20 patients the morning after LC and was not randomized formally.[2] One properly randomized trial compared pulmonary and clinical data from 40 patients after LC with 37 patients after minilaparotomy cholecystectomy, but not CC.[3] In these three trials, as in most retrospective[4-7] and prospective observational[8-9] studies, clinical endpoints were monitored, and LC compared favorably to CC with respect to length of hospital stay, weight loss, postoperative pain, and pulmonary function, indicating diminished operative trauma. However, a new therapy for cholelithiasis should be evaluated by further trials to define its indications and its benefits when compared with the standard operation of open cholecystectomy.

It is not adequate to describe the clinical significance of technologies solely in terms of case studies or empirical judgments.[10] On the other hand, randomized trials in surgery were and still are a controversial issue.[11-12] The acceptance of LC by surgeons and patients places ethical constraints on the planning of a randomized trial.[10]

As an alternative to randomization, we have planned a prospective study to measure the stress response to LC in comparison with CC (control group). A comparison of various laboratory values can be used to analyze new medical technologies.[13] Perioperative changes in circulating levels of stress hormones, blood glucose, and interleukins were measured. Postoperative pain, analgesics, and complications also were monitored.

The hypothesis to be tested proposed that the stress responses of patients to open cholecystectomy are not altered by the use of the laparoscopic technique.

PATIENTS AND METHODS

Subjects

Data were collected in a municipal hospital from May 21, 1992 through September 21, 1992. All patients with symptomatic cholelithiasis who were between 30 and 70 years of age were informed and asked for written consent the day before elective cholecystectomy. Patients with acute cholecystitis, pancreatitis, known choledocholithiasis, or history of malignant disease were excluded from the study.

Sample Method

Drinking and nutrition was withheld after 10 P.M. the night before surgery. Venous blood samples were obtained from an antecubital vein, in supine position, and after a rest of at least 5 minutes. The samples (16 mL) were drawn into plastic tubes containing 6.0 international units ammonium-heparin/2 mL blood (for glucose), plastic beads as clot activator/5 mL blood (for interleukins), 1.6 mg potassium-ethylenediamine tetraacetic acid/4 mL blood (for adrenocorticotropic hormone [ACTH] and cortisol), and in evacuated glass tubes containing 5 mg of glutathione and 9 mg of ethylene glycol tetra-acetic acid/5 mL blood (for catecholamines). The tubes for catecholamine samples were stored on ice immediately before and after blood collection, and all tubes were centrifuged within ½ hour after sampling. The supernate was stored in plastic tubes at −20 C until analyzed.

Sample Times

Preoperative baseline samples were collected between 6 and 7 P.M. the evening before and 1 hour before surgery. Further samples were taken during the dissection of the cystic pedicle, 6 hours after the end of surgery and between 7 and 7.30 A.M. 1 and 2 days after surgery.

Surgery

Both types of operations were performed by three surgeons and five residents. For CC, a standard subcostal incision was used; LC was performed by a four-trocar technique.[14] The common bile duct was examined by routine cholangiography during CC, but not during LC.

Assays

Free epinephrine and free norepinephrine concentrations in blood plasma were estimated by high-pressure liquid chromatography with amperometric detection[15] (range of normal values, based on the 90 percentile: norepinephrine = 0.10–3.1 nmol/L, epinephrine = 0.1–0.8 nmol/L, coefficients of variation 1%–3%).[16] Levels of ACTH were measured using a nonextraction sandwich radioimmunoassay (Nichols Institute, San Juan Capistrano, CA) with a normal range of 9.0 to 52.0 ng/L (2.0–11.5 pmol/L, 95% confidence limit of fasting adults, drawn between 7 and 10 A.M.) that has been evaluated previously.[17] Total plasma cortisol was measured by radioimmunoassay,[18] with a normal range of 5.6 to 20.0

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μg/dL (155–552 nmol/L). The intra- and inter-assay coefficients of variation were 3.2% and 7.8% for ACTH, and 12.4% and 16.0% for cortisol. The plasma concentration of glucose was measured automatically by a routine glucose oxidase method[19] (Glukose-Analysator 2, Beckman Instruments, Munich, Germany) with a normal reference value of 70 to 110 mg/dL (3.9–6.1 mmol/L), fasting. Interleukin-1β (IL-1β), interleukin-6 (IL-6) and interleukin-8 (IL-8) levels were determined using commercially available enzyme-linked immunosorbent assay kits (from R & D Systems, British Biotechnology, Oxford, UK). In each assay, a standard curve using recombinant human cytokine was constructed, and each sample was assayed in duplicate. The sensitivity, intra-assay variability, and inter-assay variability were 1.3 pg/mL and 8.6% for IL-1β; 1.3 pg/mL, 4.1%, and 7.8% for IL-6; and 18.1 pg/mL, 9.2%, and 12.2% for IL-8, respectively. Values from apparently healthy normal donor sera were shown to be <3.9 pg/mL for IL-1β, <6.3 pg/mL for IL-6, and ≤30 pg/mL for IL-8.

Clinical Data

Physicians and nurses were unaware of the data being monitored. Data were collected by a full-time manager. Duration, hour of operation, and drugs administered for anesthesia were recorded from the anesthetist's protocol. To permit comparison of halothane administration, different percentages of halothane volume (%vol) were converted to 1.0-%vol equivalents (e.g., 8 min 0.5 %vol. into 4 min 1.0 %vol.). Chronically administered cardiopulmonary medications were given on the morning of operation. Other chronic medications were given until the evening before cholecystectomy, and were resumed the morning after cholecystectomy. All patients received 3 × 5000 units of heparin daily for at least 3 days, beginning the morning before the operation. Routine infusions (electrolytes and glucose 5%) were administered to all patients on the day of surgery and in cases of CC, also the following day. Oral intake was allowed 1 day after LC and 2 days after CC. Pain intensity was estimated with a visual multiple-choice scale. A score of 0 represented no pain, 1 represented little pain, 2 represented moderate pain, and 3 represented intense pain. Parenteral and enteral analgesics were provided as requested by the patient, and the demands were noted by the nurses. After discharge from the hospital, a record was made of all analgesics each patient had received.

Trial Design and Statistical Analysis

In both groups, choice of the perioperative and intraoperative management were at the discretion of surgeons and anesthetists not involved in the study, and hence, were not part of the study protocol. To calculate the sample size needed to test the stated hypothesis, seven index variables were selected in advance (total plasma cortisol, ACTH, epinephrine, norepinephrine, blood glucose, IL-1β, and IL-6), and the standardized differences between the groups were calculated on the basis of findings from previous studies. Using these standardized differences, we calculated the sample size required to give the trial a power of 80% (for $\alpha < 0.05$).[20]

The response of each patient was characterized by the change in the concentration of each hormonal or metabolic variable from its respective preoperative morning baseline value. For ACTH and cortisol, the postoperative evening values were characterized by the change from their preoperative evening values.

The method of comparing changes in biochemical values was adopted to reduce the effect of variations in baseline data caused by varying degrees of preoperative illness and diurnal rhythm of secretion. Thus, the patients served as their own controls. The Mann-Whitney *U* test and Fisher's exact test were used to compare the data of the two study groups. The responses of the groups (changes from baseline) were compared at the four sampling points after the preoperative baseline samples. Thus, each time point was used in only one statistical comparison of the groups. To keep the probability of rejecting any true null hypotheses small, we applied the Bonferroni-Holm correction[21] for the multiple comparisons of hormonal and metabolic data and for comparisons of clinical endpoints between the groups. All values are presented as means (SEM) if not specified. P values are rounded to two decimal places when not quoted.

RESULTS

During the study period, 115 patients underwent cholecystectomies. According to the prospective criteria, 60 patients could join the study (40 LC and 20 CC). Two patients from the CC group with intraoperatively found choledocholithiasis and common duct exploration were excluded. Fearing vein puncture, one patient withdrew consent to the last two blood samples after CC.

Conventional cholecystectomy was performed because of prior upper-abdominal operation (n = 9), suspect of common duct stones (n = 3), thickening of the gallbladder wall (n = 5), or cystic duct stone (n = 1).

Preoperative characteristics and perioperative care of all 58 patients is described in Tables 1 and 2. There was no significant difference between the groups with respect to sex, age, weight, height, duration of cholelithiasis-related symptoms, diagnoses, and medications (Table 1). The percentage of patients with pathologically elevated gamma-glutamyl transpeptidase, more than 18 and 28 units/L (0.3 and 0.47 μkat/L) for women and men, re-

Table 1. PREOPERATIVE PATIENT CHARACTERISTICS

Variable	LC (n = 40)	CC (n = 18)	p Value
Sex (n, M/F)	9/31	8/10	0.12†
Age (years)	52.1 (1.9)	55.2 (2.9)	0.32*
Weight (kg)	72.7 (1.8)	72.7 (2.3)	0.99*
Height (cm)	165 (1.3)	168 (1.7)	0.15*
Biliary tract symptoms (wk)	251 (58)	271 (94)	0.91*
Diagnoses‡			
Arterial hypertension (%)	25	28	1.00†
Diabetes mellitus (%)	10	17	0.67†
History of heart disease (%)	5	17	0.17†
History of lung disease (%)	2.5	0	1.00†
Chronic medications‡			
Antiarrhythmic drugs (%)	0	6	0.31†
Antihypertensive drugs (%)	22.5	22	1.00†
Diuretics (%)	10	11	1.00†
Nitrates (%)	2.5	6	0.53†
Psychotropic drugs (%)	7.5	6	1.00†

Values are means (SEM) except as noted.
* Mann-Whitney *U* test.
† Fisher's exact test.
‡ Percent of patients of the respective group.
No significant differences between the groups were found.

spectively, was not significantly different between the groups ($p = 0.77$ pre- and 1.00 postoperatively by Fisher's exact test). Additionally, there was no significant difference between the groups with respect to the means of the elevated gamma-glutamyl transpeptidase values ($p = 0.75$ pre- and 0.97 postoperatively by the Mann-Whitney *U* test). Further routine laboratory values (creatinine, hemoglobin, leukocytes, potassium, sodium, platelets, partial-thromboplastin time, prothrombin time) were normal preoperatively and postoperatively and are not reported.

All patients were premedicated by mouth 1 to 3 hours before surgery, and there was no significant difference between groups in relation to premedication, operation and anesthesia data, except that higher doses of thiopental ($p = 0.04$), droperidol ($p = 0.01$), and pancuronium ($p = 0.01$) were administered in the CC group (Table 2).

Hormonal and Metabolic Responses

The CC group had significantly higher responses with respect to epinephrine on the first day after surgery ($p = 0.05$) (Fig. 1), norepinephrine on the first and second day after surgery ($p = 0.02$ and $p < 0.01$) (Fig. 2), and glucose on the first day after surgery ($p = 0.02$) (Fig. 5). The two study groups did not differ significantly in their ACTH and cortisol responses at any time point (Figs. 3 and 4).

Interleukin Responses

The changes in serum IL-1β concentrations were higher in the CC group during surgery ($p < 0.01$) and 6 hours after surgery ($p = 0.03$) (Fig. 6). Serum IL-6 increases were higher in the CC group 6 hours after surgery ($p = 0.03$) and on the first and second day after surgery ($p = 0.02$ and $p < 0.01$, respectively) (Fig. 7). There was no significant difference in the IL-8 response between LC and CC (Fig. 8).

Clinical Outcome

Six different opioid analgesics were given (mainly piritramide by intramuscular injection). All doses of opioid

Table 2. ANESTHESIA AND PERIOPERATIVE DATA

Variable	LC (n = 40)	CC (n = 18)	p Value*
Premedication			
Midazolam (%)‡	95	94	1.00†
Other benzodiazepines (%)	2.5	6	0.53†
No premedication (%)	2.5	0	1.00†
Hour of operation (h, min)	9.55 (15)	9.27 (29)	0.13
Duration of operation (min)	73 (3)	74 (6)	0.82
Duration of anesthesia (min)	87 (3)	93 (8)	1.00
Anesthetic agents			
Thiopental (%)	95	83	0.17†
Thiopental (mg/patient)	315 (10)	357 (17)	0.04
Etomidate (%)	5	17	0.17†
Fentanyl (μg/patient)	488 (11)	525 (22)	0.20
Droperidol (%)	95	94	1.00†
Droperidol (mg/patient)	9.1 (0.5)	11.2 (0.7)	0.01
Nitrous oxide (% vol)	60.7 (0.3)	59.7 (0.6)	0.21
Halothane (%)	45	50	0.71†
Halothane (min 1.0 % vol)	17 (3)	16 (3)	0.98
Pancuronium (%)	97.5	94	0.53†
Pancuronium (mg/patient)	5.2 (0.2)	6.2 (0.3)	0.01
Other curare like drugs (%)	2.5	6	0.53†
Antihypertensive drugs (%)	20	22	1.00†
Atropinic drugs (%)	60	61	1.00†
Anticholinesterase drugs (%)	62.5	67	1.00†
Naloxone (%)	2.5	6	0.53†
Intraoperative infusions			
Hydroxyethyl starch (%)	52.5	72	0.24†
Hydroxyethyl starch (ml)	450 (30)	530 (60)	0.57
Albumin human (%)	0	11	0.09†
Electrolytes (ml)	1150 (60)	1100 (120)	0.73
Postoperative infusions§			
Dextrose 5% (ml)	950 (30)	1000 (0)	0.25
Electrolytes (ml)	1450 (20)	1550 (70)	0.13

Values are means (SEM) except as noted.
* Mann-Whitney *U* test except as noted.
† Fisher's exact test.
‡ Indicates percent of patients of the respective group except as noted.
§ On the day of surgery.
Except for the doses of thiopental, droperidol and pancuronium there were no other significant differences between the groups.

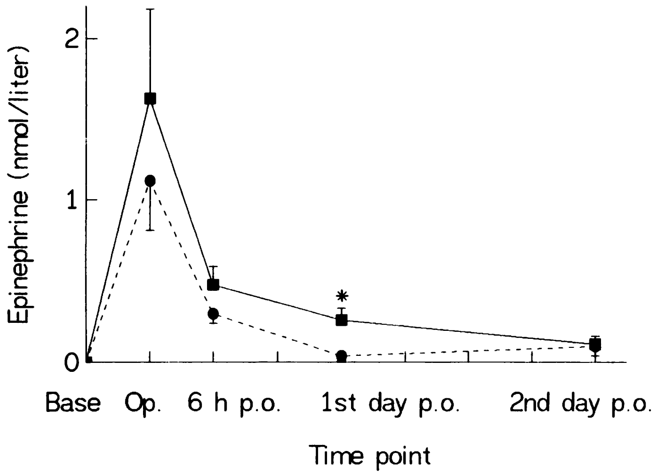

Figure 1. Perioperative changes in plasma epinephrine concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40). Base denotes preoperative, operative, intraoperative, and postoperative measurements. *p < 0.05 (Mann-Whitney *U* test and Bonferroni-Holm correction).

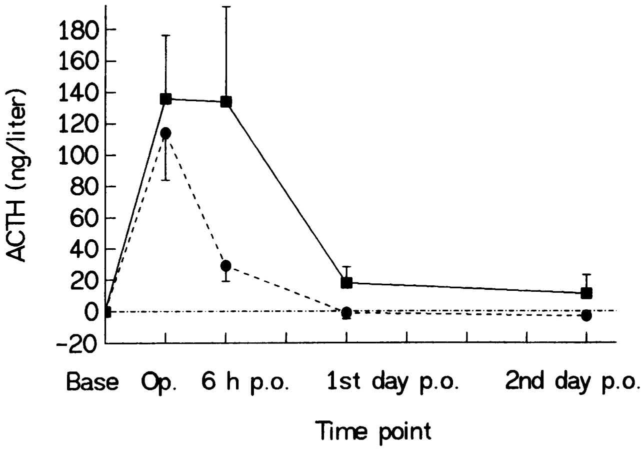

Figure 3. Perioperative changes in plasma ACTH concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40). Base denotes preoperative, operative, intraoperative, and postoperative measurements.

analgesics were converted into morphine equi-analgesic doses[22] for comparison between the groups. Aspirin-like analgesics were administered mainly as diclofenac suppositories. Additionally, only four therapeutic doses of other nonopioid analgesics (paracetamol and acetylsalicylic acid) were supplied. For comparison of aspirin-like analgesics, we considered these four doses equivalent to diclofenac. Postoperative clinical data are shown in Table 3. The CC group had an increased demand for morphine equivalents ($p < 0.001$) and higher pain scores on the day of the operation ($p < 0.001$). In both groups, there were no postoperative complications during the study period.

DISCUSSION

Because of the ethical problems associated with randomization of LC and CC, we decided to conduct a prospective trial without randomization, but with a control group. The medical staff of the municipal hospital was not involved in the particular details of the study. Medical management in this hospital was not altered by the trial, and therefore, results were considered to show biochemical and clinical responses to LC and CC under realistic hospital conditions.

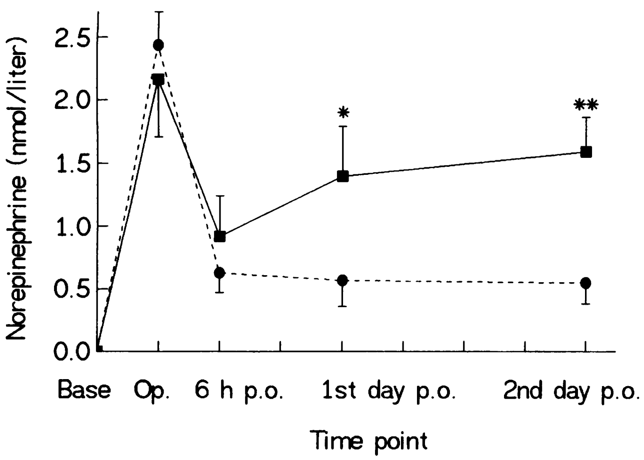

Figure 2. Perioperative changes in plasma norepinephrine concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40). Base denotes preoperative, operative, intraoperative, and postoperative measurements. *p < 0.05, **p < 0.01 (Mann-Whitney *U* test and Bonferroni-Holm correction).

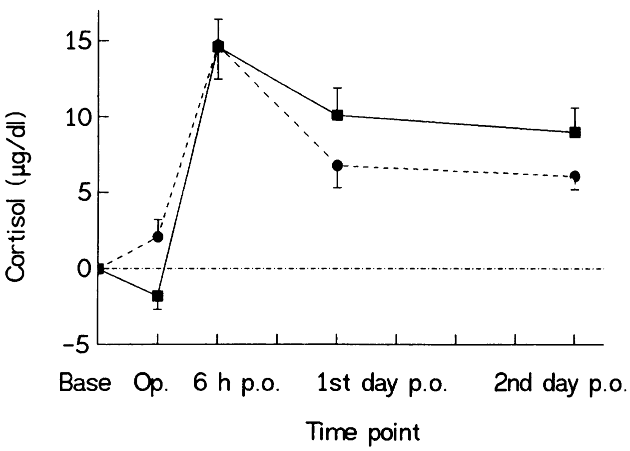

Figure 4. Perioperative changes in plasma cortisol concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40). Base denotes preoperative, operative, intraoperative, and postoperative measurements.

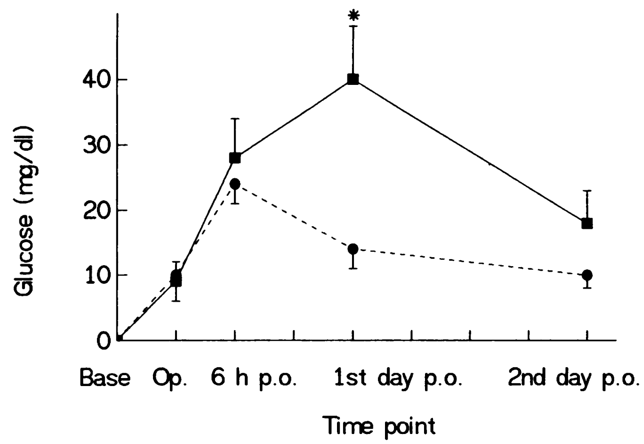

Figure 5. Perioperative changes in plasma glucose concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40). Base denotes preoperative, operative, intraoperative, and postoperative measurements. *p < 0.05 (Mann-Whitney *U* test and Bonferroni-Holm correction).

Without blinding, the two treatment modalities can be distinguished by patients and medical staff, and measurement of clinical endpoints, such as postoperative pain, analgesic demands, complications and duration of hospital stay, can be influenced subjectively. Biochemical data were used to obtain a quantitative, objective assessment and comparison of LC and CC. Laboratory personnel were not aware of the treatment provided to the patient.

Major bodily injury, whether surgical or accidental, evokes reproducible hormonal[23-26] and immunologic[27-29] responses. The magnitude of many of these changes essentially is proportional to the extent of the injury.[25-29] If, for example, LC corresponds to minor surgical trauma, this should be reflected by a minor stress response.

The indications for CC were an inevitable difference between the groups. But because there exists no evidence that these indications are responsible for specific stress responses to surgery, and because the patients in both groups had similar vital sign characteristics, baseline values and perioperative care (Tables 1 and 2), except for

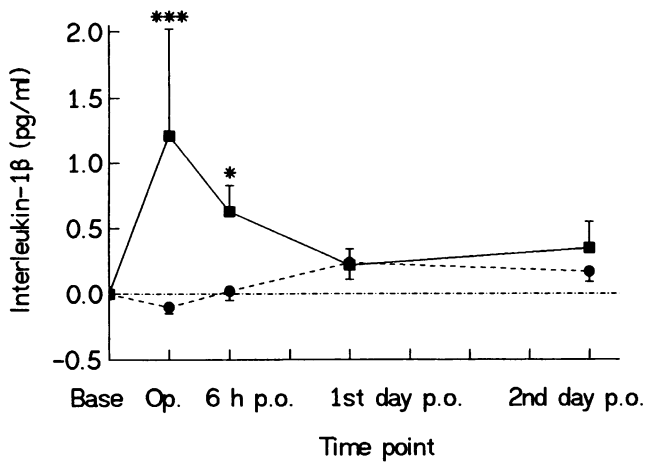

Figure 6. Perioperative changes in plasma interleukin-1 β concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40, except for 2nd postoperative day, where n = 31). Base denotes preoperative, operative, intraoperative, and postoperative measurements. *p < 0.05, ***p < 0.005 (Mann-Whitney *U* test and Bonferroni-Holm correction).

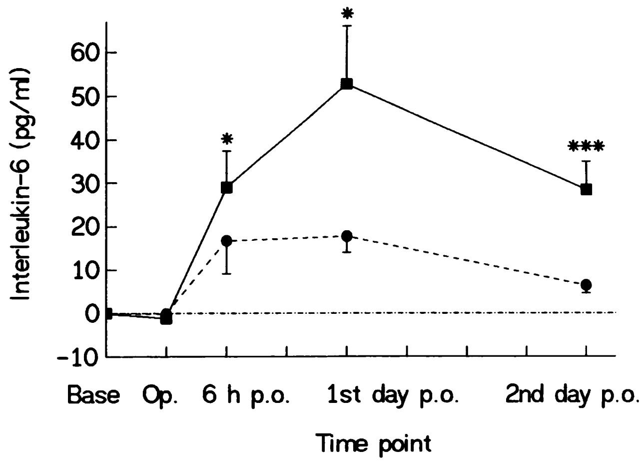

Figure 7. Perioperative changes in plasma interleukin-6 concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40, except for 2nd postoperative day, where n = 31). Base denotes preoperative, operative, intraoperative, and postoperative measurements. *p < 0.05, ***p < 0.005 (Mann-Whitney *U* test and Bonferroni-Holm correction).

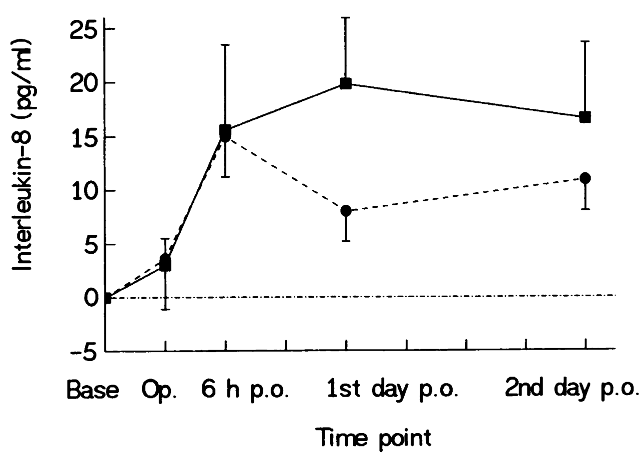

Figure 8. Perioperative changes in plasma interleukin-8 concentrations in the CC group (■, n = 18, except for 1st and 2nd postoperative day, where n = 17) and the LC group (●, n = 40, except for 2nd postoperative day, where n = 31). Base denotes preoperative, operative, intraoperative, and postoperative measurements.

Table 3. POSTOPERATIVE PAIN AND AMOUNT OF ANALGESICS

Variable	LC (n = 40)	CC (n = 18)	p Value*
Morphine equivalents	4.1 (1.2)	15.3 (2.4)	<0.001
Diclofenac equivalents	134 (26)	178 (57)	1.00
Postoperative pain scores			
Day of surgery	1.8 (0.1)	2.7 (0.1)	<0.001
1st postoperative day	1.9 (0.1)	2.2 (0.2)	1.00
2nd postoperative day	1.1 (0.1)	1.6 (0.2)	0.54

Values are means (SEM) except as noted.
* Mann-Whitney *U* test and Bonferroni-Holm correction.
Highly significant differences between the groups were found for morphine equivalents and for pain scores on the day of surgery.

lighter anesthesia and earlier oral intake in the LC group, the groups were considered comparable. Furthermore, even insignificant differences of baseline values between the groups would not have affected the significance of subsequent responses, because all patients served as their own controls and only their responses (i.e., changes from the preoperative baseline sample) were compared.

The higher doses of thiopental and droperidol that were administered in the CC group are most likely to have inhibited an even more pronounced response of catecholamines, ACTH, cortisol, and glucose in this group.[30-32] The half-life of pancuronium, given in higher doses for relaxation during CC, is about 2.3 hours. Therefore, it could have influenced the responses at most, intraoperatively, and not at the later time points of examination. Additionally, in several studies in patients, it has only been shown that pancuronium does not produce a measurable increase in circulating plasma catecholamine concentrations.[32]

Another difference between the groups was the oral intake, which was started 24 hours earlier after LC than after CC. But only the last sample on the second postoperative day could be influenced by this. Because this sample was taken in both groups after overnight fasting, the earlier oral intake probably would not have altered the data adversely.

The intraoperative cholangiogram, which was performed in the CC group only, has not been reported to change the stress response caused by surgery. Furthermore, the intraoperative sample was drawn before the cholangiogram and the first postoperative sample 6 hours after the end of surgery. Therefore, the influence of the cholangiogram on the monitored data seems to be negligible.

Only the laparoscopic technique uses carbon dioxide for peritoneal insufflation. Analysis of the effects of this highly diffusible gas has demonstrated a significant increase in intraoperative arterial carbon dioxide levels and a decrease in intraoperative pH. This was found in patients with chronic cardiopulmonary disease[33] and preoperatively compromised pulmonary function measures.[34] Because only one patient in the LC group had a history of lung disease, the differences between the groups were not attributed to the carbon dioxide insufflation.

Epinephrine, norepinephrine, ACTH, and cortisol responses were maximal intraoperatively without any significant difference between the groups until 6 hours postoperatively (Figs. 1 through 4). These early changes correspond to those documented by other authors for patients undergoing surgical stress.[26,30-31] The deeper anesthesia for CC (Table 2) may be part of an explanation for the lack of significant differences measured between the two groups intraoperatively and 6 hours postoperatively (for catecholamines, ACTH, cortisol, and glucose).[30-32]

Postoperative changes of epinephrine (first postoperative day) and norepinephrine (first and second postoperative days) were significantly decreased with LC (Figs. 1 and 2). It can be supposed that, in this later period after surgery, variations in anesthetic technique have a diminishing influence on plasma catecholamine concentrations and that the extent of surgery and the amount of pain become more significant.[32] Increasing norepinephrine concentrations were not parallel to the epinephrine responses on the first and second day after CC. This is not unusual because similar catecholamine variations have been described by others after hysterectomy and cardiac surgery[26] and probably reflect the different regulation of biosynthesis and release of these two catecholamines.

Changes of ACTH and cortisol, also in the late postoperative period (Figs. 3 and 4), have not been found to be significantly different between groups. At these time points, ACTH concentrations in both groups have returned to baseline values, as was observed in other studies in which ACTH was measured after CC.[35]

In contrast to ACTH kinetics, cortisol responses on the first and second postoperative days remained elevated in both groups relative to baseline values, according to results described previously.[35] Because ACTH has returned to baseline values at this time point, the effect of IL-6 to stimulate the release of corticosterone must be considered.[36] The postoperative cortisol changes were higher for CC, but the differences were not significant. The same was observed in another comparison of hormonal responses to various degrees of surgical trauma, where after only 1 hour postoperatively, a significant difference between the groups could be measured for cortisol; however, this could not be measured 1 and 5 days postoperatively.[25]

Significantly higher glycemia on the first postoperative day in the CC group coincided with the significantly higher concentrations of epinephrine and norepinephrine, which are known to elevate blood glucose.

Surgery causes an immune and acute-phase response, the aseptic inflammatory reaction that universally accompanies surgical trauma. Interleukin-1β and IL-6 act as potent mediators of these responses, and it has been shown that there is an early and brief IL-1β response after elective aortic surgery, followed by an IL-6 rise.[29]

Similar changes were found in this study, where IL-1β responses were significantly elevated intraoperatively and 6 hours postoperatively in the CC group in comparison with the LC group (Fig. 6). Intraoperative IL-1β concentrations reached 2.5 pg/mL during CC and thus, were comparable with the values found between 1 and 2 hours after incision in elective aortic surgery. In contrast, the IL-1β concentrations in the LC group did not rise markedly at any time point, similar to what has been found during elective hernia repair in the aforementioned study. The higher intraoperative rise of IL-1β during CC can be interpreted as a consequence of a more extended trauma, caused by the initial phase of the conventional surgery.

Interleukin-6 is released by most body tissues, and plasma concentrations may provide a measure of tissue damage during injury. This is based on recently published studies, in which the maximum serum IL-6 concentrations correlated with duration and grade of surgery.[27-29] In this study, IL-6 concentrations peaked at the first postoperative day (Fig. 7), when IL-1β has nearly returned to baseline values in both groups. This is consistent with the observation that IL-1β induces IL-6 production and release in fibroblasts, endothelial cells, keratinocytes, and peripheral blood monocytes.[37] Interleukin-6 changes showed similar kinetics in both groups, but responses were significantly higher after CC than after LC. These data are in agreement with the observation that IL-6 kinetics after inguinal hernia repair were similar to those after aortic surgery, but responses were significantly higher after aortic surgery.[29] After CC, the IL-6 concentrations found were about half as high as those measured at corresponding time points after elective aortic surgery. After LC, the IL-6 concentrations rose to maximally 19.4 pg/mL on the first postoperative day. That means that they were similar to or lower than the values found in patients who had undergone an unilateral elective hernia repair (20, 51, and 37 pg/mL at 6, 12, and 24 hours after incision).

Tissue injury stimulates directed migration and local accumulation of leukocytes at the sites of injury. Interleukin-8 has been called a cytokine, with neutrophil and T-cell chemotactic and activating functions. Intradermal injection of IL-8 caused dose-dependent accumulation of neutrophiles and lymphocytes.[38] Interleukin-8 release from human skin fibroblasts and endothelial cells has been induced by IL-1.[38-39] Therefore, we supposed IL-8 changes to be higher in the group with more extended tissue injury. Similar to IL-6, the IL-8 concentrations were elevated postoperatively (Fig. 8) and delayed relative to IL-1β, with a lower response to LC than to CC on the first and second postoperative days, thus supporting the aforementioned observations. The differences, however, of IL-8 responses were not found to be significant between the groups of this trial. This result must be seen together with the statistical calculations for sample size. Without former results of IL-8 responses to different grades of surgical stress, it was not possible to estimate the sample size needed for statistically testing the IL-8 responses with sufficient power. Thus, the failure to demonstrate a significant IL-8 difference between the groups also can be an effect of the chosen sample size.

The present trial originally was designed to examine selected parts of the hormonal, metabolic, and immunologic stress response to LC and CC, but the observed clinical differences also deserve consideration. Significantly lower pain scores on the day of operation and significantly reduced analgesic demands (Table 3) correspond to the favorable results of other trials evaluating clinical aspects of LC.[1,3,7-8]

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